

WHAT IS CLAIMED IS:

1. A composition, comprising an anti-TNF chimeric immunoglobulin chain, comprised of at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said chain capable of binding an epitope specific for human TNF $\alpha$ .

2. A composition according to claim 1, wherein said chain is a heavy chain or a light chain.

3. A composition according to claim 1, wherein said constant region is of human origin.

4. A composition according to claim 1, wherein said biological activity binding of said chain to TNF $\alpha$  has a neutralizing effect on a pathologic activity of TNF $\alpha$ .

5. A composition according to claim 1, wherein said chain has an antigen binding region which binds residues 87-108, or both 59-80 and 87-108, of hTNF $\alpha$  of SEQ ID NO:1.

6. A composition according to claim 1, wherein said chain, fragment or region does not bind to an epitope selected from the group consisting of amino acids 11-13, 37-42, 49-57 or 155-157 of hTNF $\alpha$  of SEQ ID NO:1.

7. A composition according to claim 1, wherein said chimeric immunoglobulin chain comprises two light chains and two heavy chains, each of said chains comprising at least part of a constant region and at least part of a variable region, said variable region capable of binding an epitope specific for human TNF $\alpha$ .

8. A composition according to claim 4, wherein said epitope is a neutralizing epitope of human TNF $\alpha$ , under physiological conditions.

9. A composition according to claim 1, wherein said chain does not bind to TNF $\beta$ .

10. A composition according to claim 4, wherein said variable region is of murine origin.

11. A composition according to claim 1, wherein said variable region is derived from a high affinity murine monoclonal immunoglobulin chain which binds to a neutralizing epitope of human TNF $\alpha$ .

12. A composition according to claim 11, wherein said neutralizing epitope is at least 5 amino acids selected from the group consisting of residues 87-108 and both 59-80 and 87-108 of SEQ ID NO:1.

5 13. A composition according to claim 12, wherein said epitope is selected from residues 87-108 of SEQ ID NO:1.

14. A composition according to claim 12, wherein said epitope is selected for both 59-80 and 87-108 of SEQ ID NO:1.

10 15. A composition according to claim 11, wherein said murine monoclonal chain competitively inhibits the binding of monoclonal immunoglobulin chain A2 or cA2 to TNF $\alpha$ .

16. A composition according to claim 12, wherein said murine monoclonal chain is A2.

15 17. A composition according to claim 12, wherein said murine monoclonal chain is cA2.

20 18. A composition according to claim 1, wherein said binding of said chain to human  $\alpha$ TNF has an affinity, measured as an association constant ( $K_a$ ), of at least  $1 \times 10^8$  liter/mole.

19. A composition according to claim 18, wherein said affinity is at least  $1 \times 10^9$  liter/mole.

25 20. A composition according to claim 4, wherein said chain neutralizes human TNF $\alpha$  with an ID50 of at least about 1  $\mu$ g/ml.

21. A composition according to claim 20, wherein said chain neutralizes human TNF $\alpha$  with an ID50 of at least about 100 ng/ml.

30 22. A composition according to claim 21, wherein said chain neutralizes human TNF $\alpha$  with an ID50 of at least about 15 ng/ml.

23. A composition according to claim 1, wherein said chain is in detectably labeled form.

35 24. A composition according to claim 1, wherein said chain is produced by a hybridoma or recombinantly.

✓ 25. A composition, comprising an anti-human TNF $\alpha$

chain, or a fragment or region thereof, having an anti-TNF binding region, or fragment thereof, corresponding to a

(a) murine monoclonal chain of monoclonal chain A2;  
or (b) chimeric mouse-human monoclonal chain, fragment  
or region of monoclonal chain cA2.

26. A composition, comprising a human TNF $\alpha$  peptide comprising at least 5 amino acids selected from the group consisting of amino acids residues 87-108 and both residues 59-80 and 87-108 of hTNF $\alpha$  of SEQ ID NO:1, wherein said peptide comprises an epitope of an anti-TNF immunoglobulin chain according to claim 1, or a fragment or region thereof, having anti-TNF neutralizing activity by binding to a TNF sequence other than a receptor binding locus, such that anti-TNF chain binding to a TNF receptor is substantially inhibited.

27. A composition, comprising a TNF peptide according to claim 23, consisting essentially of 3 to 22 amino acid poly-peptides having at least one sequence selected from the group consisting of:

Tyr-Ser-Gln-Val-Leu-Phe-Lys-Gly-Gln-Gly-Cys-Pro-Ser-Thr-His-Val-Leu-Leu-Thr-His-Thr-Ile, as amino acids 59-80 of SEQ ID NO:1; and

Tyr-Gln-Thr-Lys-Val-Asn-Leu-Leu-Ser-Ala-Ile-Lys-Ser-Pro-Cys-Gln-Arg-Glu-Thr-Pro-Glu-Gly as amino acids 87-108 of SEQ ID NO:1.

28. A pharmaceutical composition, comprising a chimeric chain according to claim 1, or a fragment, region thereof, or a pharmaceutically acceptable ester, ether, sulfate, carbonate, glucuronide or salt thereof, and a pharmaceutically acceptable carrier.

29. A method of use of a composition of claim 1, comprising administering to an animal a TNF inhibiting amount of a pharmaceutical composition according to claim 24.

30. A method according to claim 25, wherein said composition is administered in an amount of 0.1 to 50 mg/kg.

31. A method of use of a composition according to claim 1, for removing from a sample a TNF $\alpha$ , a fragment

thereof, or an immune complex containing said TNF $\alpha$ , the method comprising:

(a) contacting said sample to a device containing a composition according to claim 1, or a fragment or region thereof, bound to a support, such that said TNF $\alpha$ , portion thereof or immune complex reversible binds to said immobilized chain, fragment or region to provide a bound TNF $\alpha$ , portion or immune complex; and

(b) recovering said bound TNF $\alpha$ , portion or immune complex from said bound chain, fragment or region.

32. A method of use of a composition according to claim 1, comprising contacting said composition to human TNF $\alpha$  in solution, such that the contacted TNF $\alpha$  is neutralized with an ID50 of at least 1  $\mu$ g/ml.

33. A composition, comprising an anti-TNF chimeric immunoglobulin chain, comprised of at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said chain capable of binding an epitope specific for human TNF $\alpha$ .

34. A composition according to claim 33, wherein said chain is a heavy chain or a light chain.

35. A composition according to claim 33, wherein said constant region is of human origin.

36. A composition according to claim 33, wherein said biological activity binding of said chain to TNF $\alpha$  has a neutralizing effect on a pathologic activity of TNF $\alpha$ .

37. A composition according to claim 33, wherein said chain has an antigen binding region which binds residues 87-108, or both 59-80 and 87-108, of hTNF $\alpha$  of SEQ ID NO:1.

38. A composition according to claim 33, wherein said chain, fragment or region does not bind to an epitope selected from the group consisting of amino acids 11-13, 37-42, 49-57 or 155-157 of hTNF $\alpha$  of SEQ ID NO:1.

39. A composition according to claim 33, wherein said chimeric immunoglobulin chain comprises two light chains and two heavy chains, each of said chains comprising at least part of a constant region and at least part of a variable

region, said variable region capable of binding an epitope specific for human TNF $\alpha$ .

5       40. A composition, comprising a tumor necrosis factor, TNF, inhibiting effective amount of an anti-TNF compound.

      41. A composition according to claim 40, wherein said anti-TNF compound is an anti-TNF peptide.

10       42. A composition according to claim 41, wherein said anti-TNF peptide is selected from the group consisting of a fragment of a TNF receptor and an anti-TNF structural analog, said anti-TNF peptide capable of binding human TNF.

      43. A composition according to claim 41, wherein said anti-TNF peptide is a fragment of a TNF receptor.

15       44. A composition according to claim 42, wherein said structural analog is capable of binding a TNF with neutralizing activity.

20       45. A composition according to claim 42, wherein said peptide further comprises a TNF binding immunoreceptor molecule, said immunoreceptor molecule, comprising at least a portion of an immunoglobulin heavy chain CH<sub>1</sub> region, at least a portion of a hinge region and at least one immunoglobulin light chain constant region wherein at least one immunoglobulin chain is covalently linked to a non-immunoglobulin molecule capable of binding to at least one of  
25       TNF $\alpha$  and TNF $\beta$ .

30       46. A composition according to claim 45, wherein said immunoreceptor molecule further comprises at least a portion of an immunoglobulin heavy chain CH<sub>1</sub> region, at least a portion of a hinge region and at least one immunoglobulin light chain constant region.

      47. A composition according to claim 47, wherein said immunoreceptor molecule further comprises at least a portion of CH<sub>3</sub> or CH<sub>2</sub>.

35       48. A composition according to claim 46, wherein said at least one non-immunoglobulin molecule is covalently linked to the N-terminus of at least one CH<sub>1</sub> region.

49. A composition according to claim 46, wherein said at least one non-immunoglobulin molecule is covalently linked to an interior section of at least one heavy chain region.

5 50. A composition according to claim 47, wherein said the heavy chain further comprises a variable region capable of binding to a second target molecule.

51. A composition according to claim 47, wherein said the heavy chain is an IgG class heavy chain.

10 52. A composition according to claim 46, wherein said the non-immunoglobulin molecule comprises at least a portion of p55.

15 53. A composition according to claim 52, wherein the non-immunoglobulin molecule comprises sequences 2-159 of p55.

54. A composition according to claim 49, wherein the heavy chain further comprises at least about 8 amino acids of a J region.

20 55. A composition according to claim 46, said molecule further comprising at least one additional non-immunoglobulin molecule, each non-immunoglobulin molecules comprising at least a portion of p75.

25 56. A composition according to claim 52, wherein said at least one non-immunoglobulin molecule is four non-immunoglobulin molecules, each molecule comprising at least a portion of p55.

57. A composition according to claim 55, said molecule having two non-immunoglobulin molecules, each comprising at least a portion of p75.

30 58. A composition according to claim 55, said molecule having four non-immunoglobulin molecules, each comprising at least a portion of p75.

35 59. A composition according to claim 40, wherein said immunoreceptor molecule is capable of binding with high affinity to a neutralizing epitope of human TNF $\alpha$  *in vivo*.

60. A composition according to claim 33, wherein a binding affinity of said binding is at least about  $1.6 \times 10^{10}$

1/mole.

51. A composition according to claim 46, wherein said immunoreceptor molecule is capable of neutralizing TNF wherein a concentration of less than about 130 pM is capable of neutralizing about 39.2 pM human TNF $\alpha$ .

62. A composition according to claim 42, wherein said structural analog corresponds in three dimensional structure to at least a portion of a p75 or p55 extracellular region capable of binding to at least one of TNF $\alpha$  and TNF $\beta$ .

63. A method according to claim 42, wherein said structural analog further comprises at least a portion at an immunoglobulin heavy chain CH region, at least a portion of a hinge region and at least one immunoglobulin light chain constant region.

64. A composition according to claim 42, wherein said anti-TNF peptide is a fragment of a TNF receptor.

65. A composition according to claim 64, wherein said fragment comprises at least a portion of p55.

66. A composition according to claim 65, wherein said fragment comprises sequences 2-159 of p55.

67. A composition according to claim 64, wherein said fragment comprises at least a portion of p75.

68. A composition according to claim 67, wherein said fragment comprises sequences 1-235 of p75.

69. A composition according to claim 68, wherein said fragment comprises sequences 1-182 of p75.

70. A composition according to claim 69, wherein said fragment comprises sequences 1-178 of p75.

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